REMARKS

Please consider the attachment hereto in substitution for the attachment to the Response mailed November 14, 2001, which is the "DATA ATTACHMENT TO RESPONSE TO OFFICE ACTION WITH AMENDMENT, REQUEST FOR EXTENSION OF TIME AND WITHDRAWAL OF RESTRICTION REQUIREMENT", which was mailed on July 27, 2001, re-executed by the undersigned. The figure corresponding to Study 5 was inadvertently omitted in the originally-filed document and was included on page 17 of the attachment to the Response mailed November 14, 2001 and is included herewith (the attachment to the November 14, 2001 paper inadvertently omitted open boxes in the Studies 1-4 and are included in the herewith attachment).

This paper is in supplemental to the Response to the October 23, 2001 Office Action mailed November 14, 2001 and is in replacement of pages 1-4 thereof, so as to more properly parallel the claim language to the Office Action. Furthermore, claims are amended and cancelled herewith; but, these claim amendments and cancellations are not in response to any statutory rejection and are not considered narrowing. Accordingly, no estoppel arises from the herewith claim amendments, which are made to advance prosecution, and hopefully place the subject matter of elected Group I into condition for allowance, e.g., by clarifying the claims by merely providing grammatical improvement. Indeed, it is submitted that the claims, as originally presented and as herein presented, are patentably distinct over the prior art, and that these claims are and were in full compliance with the requirements of 35 U.S.C. §112. Changes to the claims, as presented herein, are not made for the purpose of patentability within the meaning of 35 U.S.C. §101, §102, §103 or §112. Rather, these changes are made simply for clarification and to round out the scope of protection to which the Applicants are entitled.

The October 23, 2001 Office Action required an election under 35 U.S.C. § 121 from among:

Group I: Claims 27-31 and 33-42, drawn to a method of treatment comprising administering a *Notch* ligand or fragments or derivatives or analogues thereof, classified in class 514, subclass 2;

Group II: Claims 7-12 to a method of tolerising T cells to an antigen or allergen using *Notch* ligand antigen presenting cells, classified in class 435, subclass 373;

Group III: Claims 13-17, drawn to *Notch* ligand conjugates, classified in class 530, subclass 350;

Group IV: Claim 18, drawn to a kit comprising *Notch* proteins or family members, classified in class 435, subclass 7.24;

Group V: Claim 19, drawn to an assay determining the effect of a compound on ligand binding to *Notch*, classified in class 436, subclass 501;

Group VI: Claim 20, drawn to a ligand capable of binding *Delta* or *Serrate*, classified in class 530, subclass 350;

Group VII: Claim 21, drawn to an assay for free *Notch, Delta* or *Serrate*, classified in class 424, subclass 9.1;

Group VIII: Claim 22, drawn to an assay for determining a compound's effect on *Notch* protein or *Notch* ligand expression or processing, classified in class 435, subclass 6;

Group IX: Claim 23, drawn to compounds which affect *Notch* or *Notch* ligand expression, classified in class 536, subclass 24.5;

Group X: Claims 24 and 25, drawn to a compound which down regulates *Delta* or *Serrate* expression, classified in class 536, subclass 24.5; and,

Group XI: Claim 32, drawn to a method of modulating expression of a functional *Notch* protein or *Notch* signaling pathways involving a *Notch* ligand, classified in class 435, subclass 377.

The invention of Group I, claims 27-31 and 33-42, drawn to a method of treatment comprising administering a *Notch* ligand or fragments or derivatives or analogues thereof, classified in class 514, subclass 2, is elected.[1] Reconsideration and withdrawal of the restriction requirement are respectfully requested in view of the remarks herewith.

The present invention relates to the use of therapeutic compounds in the modification of T cell activation. In particular, the elected invention relates to the use of *Notch* ligands in the treatment of T cell mediated disease or infection. The invention also relates to the therapeutic use of such compounds to treat, for example, graft rejection, autoimmunity, allergy, asthma, infectious diseases and tumor induced aberrations to the T cell system.

The present claims, therefore, represent a web of knowledge and continuity of effort that merits examination in a single application. Indeed, the claims of Groups II, IV, VIII and XI are

[1] In view of the amendments herewith, it is respectfully submitted that Group I now includes claims 27, 28, 29, 31 and 33-39. Claims 40 and 41 are dependent upon claim 32; and, the undersigned respectfully cannot locate a claim 42.

related since the claims of all four groups are classified in class 435; and, the claims of Groups III and VI are classified in class 530, subclass 350. The claims of Groups IX and X are classified in class 536, subclass 24.5. The claims of Group I and II are related as both relate to a therapeutic method involving *Notch* ligands. Finally, the claims of Groups VII and VIII, although arguably classified in different classes, relate to assays involving *Notch* or *Notch* ligands. Indeed, all the claims involve the *Notch* receptor family or *Notch* ligands.

In this regard, the Examiner's attention is respectfully directed to MPEP § 808.02 which states, ". . . restriction is not (emphasis added) required unless one of the following reasons appears:

1. Separate classification;
2. Separate status in the art; or
3. Different field of search . . ."

Contrary to the guideline provided by the MPEP, Groups II, IV and XI, Groups III and VI, Groups VII and VIII, and Groups IX and X are, respectively, in the same classes. Further, Groups VII and VIII involve the same status in the art. Importantly, the claims in all eleven Groups involve *Notch* or *Notch* ligands, thereby encompassing the same field of search. As an example, claim 23 in Group IX is a product detected by a particular assay which may be used in Group I and should, consequently, be searched concurrently with the claims of Group I. Thus, restriction is not appropriate.

Additionally, the Examiner's attention is further respectfully invited to review the text of MPEP § 803 which in part states:

> If the search and examination of an entire application
> can be made without serious burden, the Examiner
> must examine it on the merits ... (emphasis added).

A search of Group I will necessarily involve a search of the non-elected groups, which should therefore be rejoined to elected Group I.

The result of the present restriction requirement are inefficiencies and unnecessary expenditures by both the Applicants and the PTO and extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional applications

filed); and restriction has not been shown to be proper, especially since the requisite showing of serious burden has not been made in the Office Action and there are relationships between the claims of all nine Groups. Indeed, the search and examination of each Group is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of the entire application can be made without undue burden on the Examiner. All of the preceding, therefore, mitigate against restriction.

In view of the foregoing, reconsideration and withdrawal of the restriction requirement and favorable examination of Claims 7-25 and 27-41 on the merits are respectfully requested.

Certified copies of the documents from which this application claims foreign priority under 35 U.S.C. § 119 (a)-(d) will be filed in due course.

REQUEST FOR INTERVIEW

If the restriction requirement is maintained as to Group I, prior to issuance of a first Office Action on the merits, an interview is respectfully requested, especially in view of the prior submission of data to substantiate the claimed invention; and therefore, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

Respectfully submitted,

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Appendix: Marked Version of Amendments to Show Changes

IN THE CLAIMS

Please amend the claims, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, as follows:

27. (Amended) A method of treating T-cell mediated disease or infection comprising administering a medicament comprised of a *Notch*[-]ligand to a patient in need thereof.

29. (Amended) The method of treating T-cell mediated disease or infection of any of claims 27 or 28, wherein the *Notch*[-]ligand is selected from Serrate, Delta or fragments, derivatives or analogs thereof.

32. (Amended) A method of modulating expression of a functional *Notch*[-]protein or *Notch* signaling pathways involving a *Notch*[-]ligand.

38. (Amended) The method of treating T-cell mediated disease or infection of any of claims 27 or 28, or 33-37 wherein the *Notch*[-]ligand is [selected from] Serrate, or Delta.

39. (Amended) The method of treating T-cell mediated disease or infection of any of claims 33-37, wherein the *Notch*[-]ligand is [selected from] Serrate, or Delta, or fragments, derivatives or analogs thereof.

40. (Amended) The method of [any one of] claim[s] [30-]32 wherein the *Notch*[-]ligand is [selected from] Serrate, or Delta, or fragments, derivatives or analogs thereof.

41. (Amended) The method of [any one of] claim[s] [30-]32 wherein the *Notch*[-]ligand is [selected from] Serrate, or Delta.

PATENT
674525-2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants(s)	:	Lamb et al.
U.S. Serial No.	:	09/310,685
Filing Date	:	May 4, 1999
Examiner	:	A. DeCloux
Art Unit	:	1644
For	:	**NOTCH**

745 Fifth Avenue
New York, NY 10151

FACSIMILE

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Thomas J. Kowalski, Reg. No. 32,147
Type or print name of person signing certification

Thomas J. Kowalski
Signature

December 4, 2001
Date of Signature

DATA ATTACHMENT TO
SUPPLEMENTAL RESPONSE TO OFFICE ACTION & AMENDMENT
WITH REQUESTS FOR
WITHDRAWAL OF RESTRICTION REQUIREMENT
AND INTERVIEW

Assistant Commissioner for Patents
Washington, D.C. 20231
Dear Sir:

This is also in response to the October 23, 2001 Office Action.

In order to demonstrate further the use of Notch ligands in the control of T-cell mediation of immune responses, the following studies have been carried out by Applicants or Applicants' assignee, in the ordinary course of business.

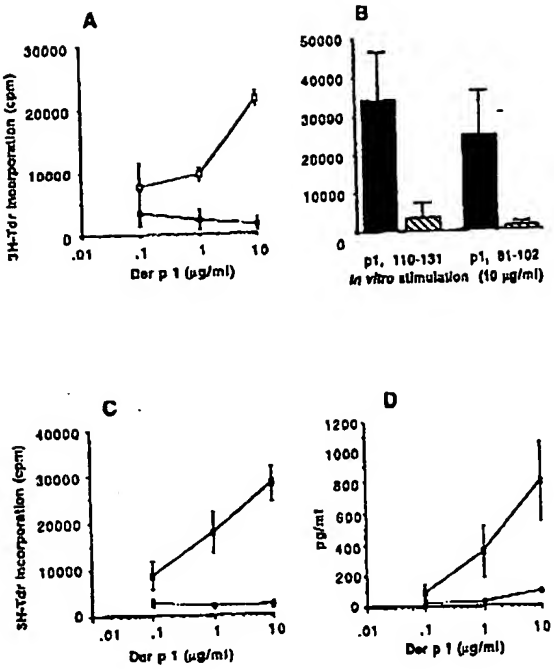
Study 1

Notch ligand expressing antigen-presenting cells inhibit T-cell immunity to the antigen presented.

(A) Mouse antigen-presenting cells (APC) were infected with Notch ligand gene *Serrate1* (•) or control (□) virus, pulsed with dust mite antigen p1, 110-131 peptide and injected into naïve C57BL/6J mice and two weeks later mice were immunized with 50 μg House Dust Mite (HDM) antigen Der p 1/Complete Freund's Adjuvant (CFA). Lymph node (LN) cells were cultured *in vitro* with Der p 1 and T-cell proliferation was measured and the results presented as mean c.p.m. ± SD of four mice per group.

(B) LN cells from mice primed as described above [*Serrate1*$^+$ APC (shaded bars) or a control APC (closed bars)] were cultured *in vitro* with the Der p1 peptides p1, 110-131 or p1, 81-102 at 10μg/ml and proliferation measured. The supernatants from these assays were collected at 24 h and assessed for IL-2 production (C), while 48 h supernatants were assessed for the presence of IFN-γ (D).

This study shows that antigen-presenting cells expressing Notch ligand are able to inhibit T-cell activity to antigen.

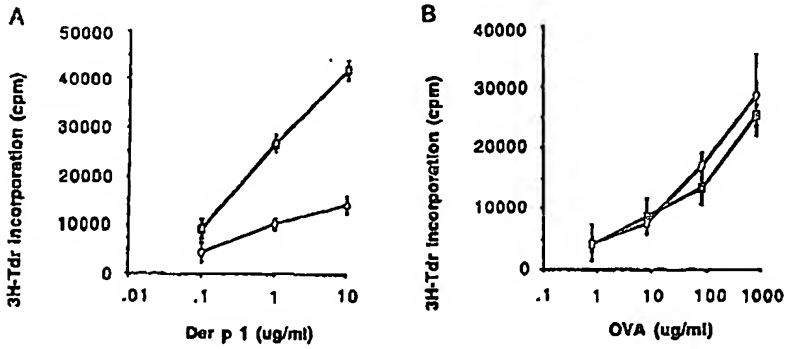

A
30000
20000
10000
0
3H-Tdr incorporation (cpm)
.01
.1
1
10
Der p 1 (µg/ml)
B
50000
40000
30000
20000
10000
0
p1, 110-131
p1, 81-102
In vitro stimulation (10 µg/ml)
C
40000
30000
20000
10000
0
3H-Tdr incorporation (cpm)
.01
.1
1
10
Der p 1 (µg/ml)
D
1200
1000
800
600
400
200
0
pg/ml
.01
.1
1
10
Der p 1 (µg/ml)

Study 2

Immunization with Notch ligand expressing antigen-presenting cells pulsed with specific peptide induces antigen specific but not global suppression of immunity.

(A) APC were infected with *Serrate1* (○) or control (□) virus pulsed with p1, 110-131 and 2 weeks later the mice were immunized with 50 μg Der p 1/CFA. LN cells were cultured *in vitro* with Der p 1 and proliferation was measured and the results presented as mean c.p.m. ± SD of four mice per group. (B) Mice were injected with *Serrate1*$^+$ APC pulsed with p1, 110-131 as described above but then immunized with OVA/CFA. LN cells were re-stimulated with OVA *in vitro* and proliferation measured as above.

This study shows that antigen-presenting cells expressing Notch ligand in the context of one antigen are able to inhibit the immune response in relation to that specific antigen, but without global suppression of immunity (ie immune response to other antigens, such as the ovalbumin used here, is not significantly affected).



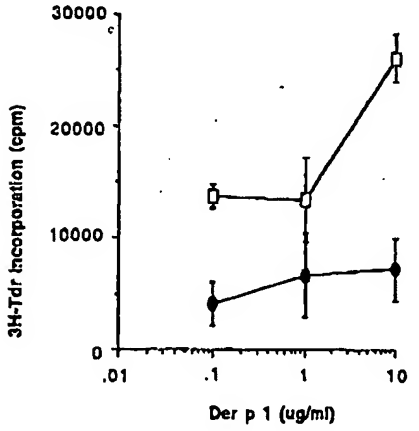
These experiments showed the ability of Notch ligand to induce tolerance in a prophylactic protocol. However, Notch ligand can also induce tolerance to an established immune response as shown in Study 3 below.

Study 3

Notch ligand expressing antigen-presenting cells inhibit established immune responses.

Naïve mice were immunized with 50 µg Der p 1/CFA and 3 weeks later they were injected with p1, 110-131-pulsed DC infected with either *Serrate1* (•) or control (□) virus. Two weeks later mice were reimmunized with 50 µg Der p 1/incomplete Freund's adjuvant and the proliferative response of LN cells to re-stimulation with Der p1 measured as described in Study 1 (A) above.

This study shows that Notch ligand can also induce tolerance to an established immune response.

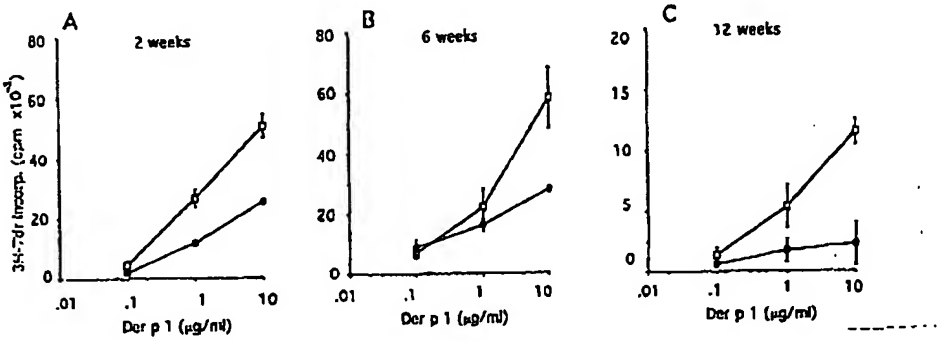


Study 4

Inhibition of T-cell responses induced by Notch ligand expressing antigen-presenting cells is long lived.

p1, 110-131 peptide-pulsed APC infected with either *Serrate1*$^{+}$ (•) or control (□) virus were injected into naïve C57BL/6J mice and (A) 2, (B) 6 or (C) 12 weeks later mice were immunized with Der p 1/CFA and proliferation determined as described in Study 1(A) above.

This study shows that Notch ligand inhibition of T-cell responses is long lived.



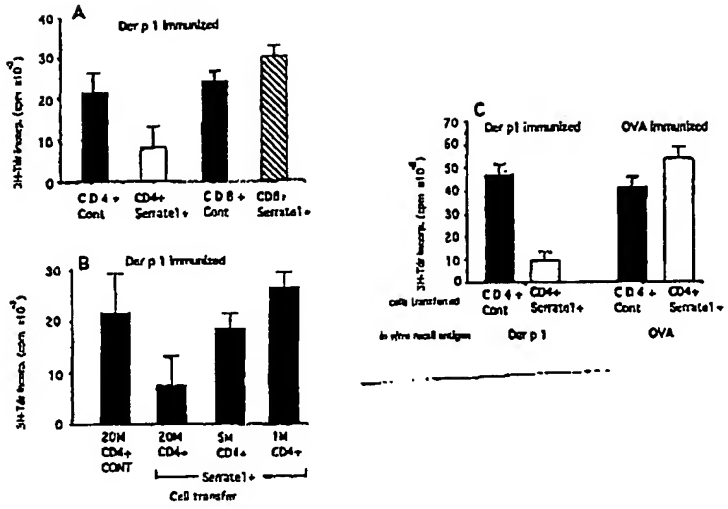
Study 5

Antigen-specific tolerance induced by Notch ligand expressing antigen-presenting cells can be transferred to naïve mice by T-cells.

(A) p1, 110-131 peptide-pulsed APC infected with either *Serrate1* or control virus were injected into naïve C57Bl/6J mice and two weeks later CD4+ or CD8+ T cells were isolated from spleens and adoptively transferred to naïve mice at 2 x 10^7/mouse. On the same day mice were immunized with 50 µg Der p 1/CFA and 1 week later LN cells were cultured *in vitro* with Der p 1. Results are presented for proliferation (mean c.p.m ± SD of four mice per group) measured at 72 h in response to re-stimulation with 10 µg/ml Der p1. Transfer of T-cells from mice injected with *Serrate 1*$^+$ (open and shaded bars) or control, (solid and grey bars) DC is shown.

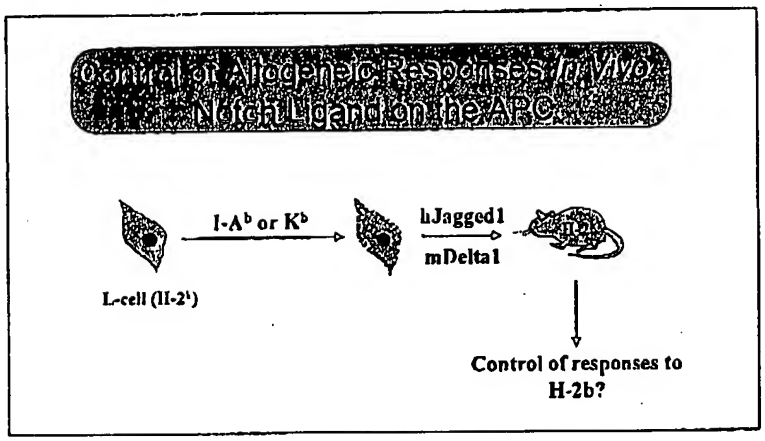
(B) p1, 110-131 peptide-pulsed APC infected with *Serrate1* (grey bars) or control (solid bars) virus were injected into naïve C57Bl/6J mice and two weeks later CD4+ - T cells were isolated from spleens and transferred to naïve mice (2x10^7 control CD4+ T cells or 2 x 10^7, 5 x 10^6 or 1 x 10^6 CD4+ T cells from *Serrate 1*$^+$ APC injected mice) which were immunized with 50 µg Der p 1/CFA on the same day. Results are presented for proliferation of LN cells (mean c.p.m. ± SD of four mice per group) measured at 72 h in response to re-stimulation with 10 µg/ml Der p1. (C) p1, 110-131 peptide-pulsed APC infected with *Serrate1* (open bars) or control (solid bars) virus were injected into naïve C57BL/6J mice and 2 weeks later CD4+ T cells were isolated from spleens and 2 x 10^7 cells transferred to naïve mice which were immunized with 50 µg Der p1/CFA or OVA/CFA on the same day. Results are presented for proliferation of LN cells (mean c.p.m. ± SD of four mice per group) measured at 72 h in response to re-stimulation with 10µg/ml Der p1 or 800 µg/ml OVA.

This study shows that antigen-specific tolerance induced by Notch ligand can be transferred to naïve mice by T-cells (infectious tolerance).


A
Der p 1 Immunized
CD4+ Cont
CD4+ Serrate1+
CD8+ Cont
CD8+ Serrate1+
B
Der p 1 Immunized
20M CD4+ CONT
20M CD4+
5M CD4+
1M CD4+
Serrate1+
Cell transfer
C
Der p1 immunized
OVA immunized
CD4+ Cont
CD4+ Serrate1+
Der p 1
OVA

Study 6

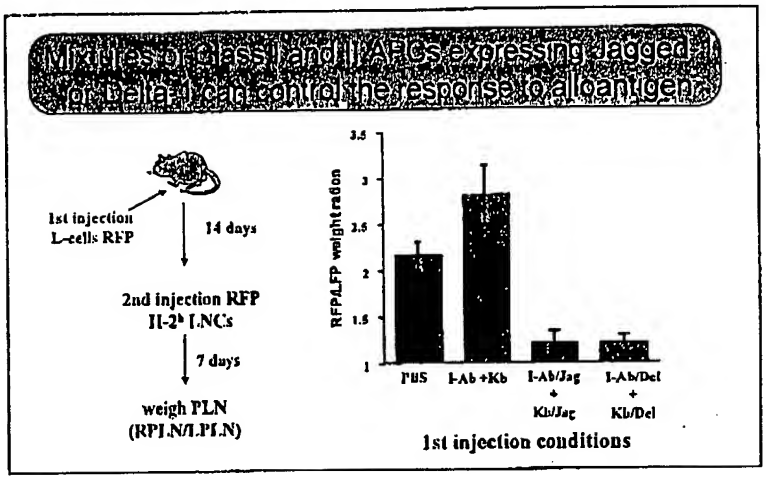
L-cells are a mouse cell line expressing the H-2^k MHC haplotype. These cells were transfected with Class I or class II MHC molecules of the H-2^b haplotype and then further transfected with the Notch ligands Jagged or Delta. These cells were then injected into H-2^k mice to see if they would tolerise the mice to a subsequent transplant of H-2^b cells.



The modified L-cells were injected into the right foot pad of an H-2^k mouse. 14 days later lymph node cells from an H-2^b mouse where injected into the right foot pad. After a further 7 days the popliteal lymph nodes (PLN) draining the right (R) and left (L) feet were removed and weighed and the R/L weight ratio calculated as a measure of the immune response to the transplanted cells. In the first injection the mice received either:

- saline control (PBS)
- the I-A^b & K^b transfected L-cells
- the I-A^b + Jagged & K^b + Jagged transfected L-cells
- the I-A^b + Delta & K^b + Delta transfected L-cells

It is clear from the results below that the Notch ligands have almost completely suppressed the immune response to a subsequent challenge with "foreign" cells. Further studies have shown that this tolerance is long-lived and specific. The H-2^k-mice tolerised to H-2^b will mount a perfectly normal immune response when challenged with cells from a third strain of mice (H-2^s haplotype).



Summary

To summarise, taken together with the examples already presented in the present application, these results show that Notch ligands can be used to control T-cell activity in a uniquely antigen-specific manner. The same effect has been demonstrated *in vitro* and *in vivo*, in mouse and human cells, and with a wide range of very different types of antigens including:

- soluble antigens (Der p1 and individual epitopes thereof from the House Dust Mite);
- capsid antigen (Haemagglutinin (HA) from the influenza virus); and

- whole allograft cells from mice displaying a range of cell surface antigens in the form of Class I and Class II MHC molecules presenting a range of cellular and exogenous peptides.

This shows that the principle involved is of entirely general application. Moreover the range of different antigens used shows that the mechanism involved relates to underlying T-cell activity and is not restricted to any particular disease or indication as such.

Respectfully submitted,

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